

 Walter  
Cybulski/DC/USEPA/US  
10/19/2006 08:50 AM

To NCIC HPV@EPA  
cc Jeffrey Taylor/DC/USEPA/US@EPA, EClark@velsicol.com  
bcc  
Subject AR201- Velsicol Chemical Corporation - Delivery of  
Response to EPA comments on Test Plan for Dipropylene  
Glycol Dibenzoate (CAS# 27138-31-4)

----- Forwarded by Walter Cybulski/DC/USEPA/US on 10/19/2006 08:26 AM -----



"Clark, Emily"  
<EClark@velsicol.com>  
10/18/2006 04:52 PM

To Walter Cybulski/DC/USEPA/US@EPA  
cc  
Subject EPA Correspondence to Velsicol Chemical Corporation  
Regarding Dipropylene Glycol Dibenzoate

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Dear Mr. Cybulski:

I recently received the EPA's letter to Velsicol Chemical Corporation regarding the status of our HPV submission for dipropylene glycol dibenzoate (CAS# 27138-31-4). I would like to note that the correspondence was addressed to Neal Netzel, who is no longer with the company. Please replace Mr. Netzel's name with my own for any further correspondence regarding this issue.

I have attached to this email, Velsicol's February 27, 2002, response to EPA's comments of January 28, 2002. In addition, I have included the DHL details confirming EPA's receipt of this letter.

Velsicol has been an active participant in EPA's HPV program and believes we have completed all necessary testing for the program and that this correspondence represents the final data package relative to this substance.

Please feel free to contact me if you have any questions or require anything further.

Best regards,

Emily Clark  
Global Product Safety Manager  
Velsicol Chemical Corporation  
10400 W. Higgins Road, Suite 600  
Rosemont, Illinois 60018  
1.847.635.3454



eclark@velsicol.com Dipropylene Glycol Dibenzoate Response to EPA.pdf



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2006 NOV -9 AM 7:37

February 27, 2002

Oscar Hernandez, Director  
Risk Assessment Division  
U.S. Environmental Protection Agency  
1200 Pennsylvania Avenue NW  
Washington D.C. 20460

Mr. Hernandez:

Please find below a response to your January 28, 2002 letter describing EPA's comments to Velsicol Chemical Corporation's HPV Challenge Robust Summary submission for Dipropylene Glycol Dibenzoate.

**□ Photodegradation, Stability in Water and Fugacity**

EPA's Comment:

"The submitter provided calculated photodegradation, stability in water, and transport (fugacity) data on diethylene glycol dibenzoate and triethylene glycol dibenzoate to satisfy the environmental fate end points, instead of collecting data on dipropylene glycol dibenzoate. . . . The submitter needs to explain why it decided to take this approach instead of providing data for dipropylene glycol dibenzoate. EPA prefers that the submitter provide measured data for photodegradation and stability in water where possible, and estimated data for transport and distribution (fugacity) for dipropylene glycol dibenzoate."

Velsicol Chemical Corporation's Response:

Diethylene glycol dibenzoate, triethylene glycol dibenzoate and dipropylene glycol dibenzoate each contain the same functional groups and therefore any differences in physical and chemical properties will be due primarily to differences in molecular weight.

It was therefore decided to test the lowest molecular weight and the highest molecular weight member of the series and read across the data to assess the physicochemical properties of the middle member of the series, dipropylene glycol dibenzoate. The approximate molecular weight of each chemical is shown below:

Diethylene Glycol Dibenzoate	Molecular Weight	106
Dipropylene Glycol Dibenzoate	Molecular Weight	134
Triethylene Glycol Dibenzoate	Molecular Weight	150

**□ Developmental Toxicity**

EPA's Comment:

"The summary should provide a single developmental NOAEL based on the most sensitive developmental effect—a NOAEL of 250 mg/kg/day and a LOAEL of 500 mg/kg/day based on developmental delay indicated by incomplete ossification of sternebrae. In addition, the summary should provide the incidence of incomplete ossification of the 5<sup>th</sup> and 6<sup>th</sup> sternebrae and its statistical significance."



□ **Daphnia Toxicity**

EPA's Comment:

"The missing required data elements are water hardness and information on the toxic concentration for this endpoint. The 48-hour LC<sub>50</sub> daphnia value is expressed as the percent of the loading concentration. However, EPA suggests calculating the mean measured value using the reported percent concentration of each sample tested."

Velsicol Chemical Corporation's Response:

Water hardness of batches of Elendt medium are measured after preparation and results show that hardness typically falls in the range of 220 to 280 mg/l as CaCO<sub>3</sub>. The 48-hour EC<sub>50</sub> of dipropylene glycol dibenzoate to *Daphnia magna* based on the geometric means of the measured concentrations of dipropylene glycol dibenzoate, is 4.3 mg/l (95% confidence limits, 2.89-5.82 mg/l). See Table 1.

□ **Algae Toxicity**

EPA's Comment:

"The 96-hour EC<sub>50</sub> value for the *Selenastrum capricornutum* test was inadequate for this endpoint because concentrations, though apparently measured, were not provided in the robust summary. In order to determine the toxicity for the algal end points (biomass and growth rate), all percent loadings of the tested samples and/or converted mean measured concentrations must be presented. Other required data elements missing are water hardness and pH."

Velsicol Chemical Corporation's Response:

pH measurements of the contents of each flask show that pH values ranged from 7.6 to 7.8 at the start of the test and from 7.3 to 7.4 at the end of the test. The total hardness of the nutrient medium used in algal tests is measured at intervals. The preparation records show its hardness is quite low and typically falls in the range of 25-30 mg/l as CaCO<sub>3</sub>. The 96-hour EC<sub>50</sub> of dipropylene glycol dibenzoate for biomass and growth rate reduction of the alga *Selenastrum capricornutum*, based on the geometric means of the measured concentrations of dipropylene glycol dibenzoate, were 0.63 mg/l and 2.48 mg/l respectively. See Table 2.

Please include these data points with our initial robust summary submission for dipropylene glycol dibenzoate dated February 23, 2001. If you have any further questions or comments, feel free to contact me at (847) 635-3454.

Regards,

\_\_\_\_\_  
Emily Clark  
Regulatory Compliance Specialist

Attachment

Velsicol Chemical Corporation's Response:

The incidence of fetuses/litters with incomplete ossification of the 5<sup>th</sup>/6<sup>th</sup> sternebrae is presented below. This data does not readily lend itself to statistical analysis and we do not think that it is necessary as the finding is not considered to represent an adverse effect of development and does not affect in any way the no-observed-effect-level.

Group Dose (mg/kg/day) Number Examined	Fetuses				Litters			
	1 0	2 250	3 500	4 1000	1 0	2 250	3 500	4 1000
	158	161	163	155	22	22	22	22
Incomplete ossification Sternebrae – 5 <sup>th</sup> and/or 6 <sup>th</sup>	77	68	104	104	19	18	21	21

In this study the overall developmental NOAEL was considered to be 500 mg/kg/day on the basis of the most sensitive parameter (an increase in fetuses/litters with cervical ribs in the 1000 mg/kg/day group). An association between treatment at 1000 and 500 mg/kg/day and the greater number of fetuses with incomplete ossification of the 5<sup>th</sup> and/or 6<sup>th</sup> sternebrae cannot be discounted, particularly since a delay in ossification would be expected to be the most sensitive marker of an effect on pre-natal development where treatment has continued through to the day before sacrifice (treatment period: Days 6-19 of gestation). The assessment of fetal ossification on Day 20 of gestation represents a snapshot in time as the ossification will continue as the animals grow and mature. Although the relationship of these findings to treatment is uncertain, they are considered to be transient in nature, rather than representing permanent structural changes, and therefore are considered to be of no long-term toxicological importance.

The increase in cervical ribs at 1000 mg/kg/day is considered to be of greater toxicological significance as it occurred at a dosage which has not produced any detectable signs of maternal toxicity; however, cervical ribs were only found in a small number of fetuses (10/155) at the limit dosage of 1000 mg/kg/day and there was no concomitant change in vertebral configuration.

In conclusion, the NOAEL for all aspects of pre-natal development is concluded to be 500 mg/kg/day.

□ **Reproductive Toxicity**

EPA's Comment:

"Estimated doses associated with the various dietary concentration levels need to be provided in the robust summary."

Velsicol Chemical Corporation's Response:

Achieved dosages – group mean values (mg/kg/day) for animals before pairing (F0)

Group:	1	2	3	4
Dietary Concentration (ppm):	0	1000	3300	10000

	<b>Male</b>	<b>Female</b>
Group 1:	0	0
Group 2:	52.7 – 113.5	63.5 – 112.9
Group 3:	174.1 – 380.3	211.9 – 384.9
Group 4:	534.2 – 1160.7	654.3 – 1169.3

Achieved dosages – group mean values (mg/kg/day) for females during gestation and lactation (F0)

Group:	1	2	3	4
Dietary Concentration (ppm):	0	1000	3300	10000

Period of Study	Group		
	2	3	4
<b>Gestation</b>			
Days 0-5	106	348	989
Days 6-12	80	265	834
Days 13-19	70	256	770
<b>Lactation</b>			
Days 1-3	121	363	1406
Days 4-6	149	495	1567
Days 7-13	175	606	1837

Achieved dosages – group mean values (mg/kg/day) for animals before pairing (F1)

Group:	1	2	3	4
Dietary Concentration (ppm):	0	1000	3300	10000

	<b>Male</b>	<b>Female</b>
Group 1:	0	0
Group 2:	59.2 – 162.9	73.0 – 171.7
Group 3:	195.6 – 547.4	241.4 – 611.1
Group 4:	597.3 – 1759.5	745.2 – 1764.9

Achieved dosages – group mean values (mg/kg/day) for females during gestation and lactation (F1)

Group:	1	2	3	4
Dietary Concentration (ppm):	0	1000	3300	10000

Period of Study	Group		
	2	3	4
<b>Gestation</b>			
Days 0-5	86	282	864
Days 6-12	82	264	825
Days 13-19	76	263	821
<b>Lactation</b>			
Days 1-3	88	344	1074
Days 4-6	123	430	1439
Days 7-13	176	654	2086

#### ☐ Fish Toxicity

##### EPA's Comment:

"The following missing required data elements need to be submitted are: pH, DO, and total organic carbon (TOC)."

##### Velsicol Chemical Corporation's Response:

Typical water quality characteristics included:

pH	7.4 – 8.0
Dissolved oxygen	7.3 – 8.4 mgO <sub>2</sub> /l
Total organic carbon	2.3 mg/l

**Table 1**  
***Daphnia magna*, 48-h EC<sub>50</sub>**

% Immobilisation	Nominal WAF (mg/l)	Measured Levels (mg/l)	
		Dibenzoate (Fresh)	Dibenzoate (Old)
10	1.0 (0.248)	0.339	0.181
5	2.2 (0.733)	0.895	0.601
25	4.6 (1.322)	1.415	1.235
40	10 (3.627)	4.940	2.663
85	22 (7.331)	8.869	6.060
60	46 (5.164)	6.330	4.213
90	100 (11.678)	19.270	7.077
48 h EC <sub>50</sub> based on nominal dibenzoate levels = 19.31 mg/l (95% c.i. = 13.1 – 28.5 mg/l)			
EC <sub>50</sub> based on geometric means of measured dibenzoate levels = 4.3 mg/l (2.89 – 5.82 mg/l)*			

Fresh / old – freshly prepared media and "old" media at the end of the test

0 – Geometric mean of measured dibenzoate concentrations

\* Logistic regression, Williams (1986), Interval estimation of medial lethal dose.  
Biometrics, 42, 641-645.

**Table 2**  
***Selenastrum capricornutum*, 96-h EC<sub>50</sub>**

% Inhibition at 96 h		Nominal WAF (mg/l)	Measured Levels (mg/l)	
Biomass	ASGR		Dibenzoate (Fresh)	Dibenzoate (Old)
15	0	0.1 (0.070)	0.099	0.050
18	0*	0.22 (0.157)	0.213	0.115
23	0*	0.46 (0.265)	0.376	0.187
44	8	1.0 (0.683)	0.876	0.533
82	36	2.2 (1.596)	1.929	1.321
93	62	4.6 (3.196)	3.363	3.038
97	77	10 (5.929)	6.858	5.125
96 h EC <sub>50</sub> (biomass) based on nominal dibenzoate levels = 0.95 mg/l				
96 h EC <sub>50</sub> (growth rate) based on nominal dibenzoate levels = 3.6 mg/l				
96 h EbC <sub>50</sub> (biomass) based on geometric means of measured dibenzoate levels = 0.63 mg/l**				
96 h ErC <sub>50</sub> (growth rate) based on geometric means of measured dibenzoate levels = 2.48 mg/l **				

ASGR – Average Specific Growth Rate

0 – Geometric mean of measured dibenzoate concentrations

\* stimulation (1%) compared to controls

\*\* Logistic regression, Willimans (1986), Interval estimation of medial lethal dose.  
Biometrics, 42, 641-645.

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